

Sovereign Pharmaceuticals, Inc.

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October 22, 1999

Food & Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: **Comments concerning the draft, "Guidance For Industry, ANDAs: Blend Uniformity Analysis", Docket Number 99-D-2635.**

Dear Sir or Madame,

The Food & Drug Administration (FDA) has recently published a draft guidance for industry entitled: "ANDAs: Blend Uniformity Analysis" (BUA) that requires blend uniformity testing be performed on all commercial batches to show that the process is in control. It is the opinion of Sovereign Pharmaceuticals that the in-process controls and tests already in place are more than adequate to assure uniformity and homogeneity. **This guidance only increases the already sizeable regulatory burden without adding value to the product, and should be withdrawn.**

While giving the FDA's perspective at the NAPM-GPIA-NPA-FDA Fall Technical Meeting this week, speaker Dr. David Gill stressed the FDA's position that the industry needs to provide **added assurance** that each product meets the requirements set forth in the regulations. If a process is "in control" it can be validated. **Validation provides the "added assurance."** Once a process is validated, no value is added to the product by requiring the industry to revalidate the process forever via blender sampling and testing.

Dr. Gill also pointed out that a very large number of recalls were due to content uniformity issues. In the February 1999, issue of "The Gold Sheet" all of the drug product recalls that occurred in 1998 were listed. **In 1998, out of the 154 recalls listed, only three were due to Content Uniformity failures!** The table below summarizes the results from "The Gold Sheet" for the past four years.

	Total Recalls	Recalls - Content Uniformity Failures
1998	154	3
1997	208	6
1996	204	5
1995	189	8
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Totals	755	22 or 2.9%

We live in an imperfect world and no matter how many controls the FDA successfully imposes on the industry, there will always be exceptions for regulators to focus on. This guidance only increases regulatory burden without adding value to the product; and, as mentioned before, should be withdrawn.

99D-2635

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Because generic products follow the innovator products to market, their quality and safety track record is inherently better. On Tuesday, while speaking at the above mentioned Fall Technical Meeting, Dr. Roger Williams, Office of Pharmaceutical Sciences, FDA, commented that "the generic industry can frequently make a better product" (than the innovator's). It follows that to be "approved", generic drug products must be as good or better than those produced by the innovators. So why is the FDA specifically targeting the generic industry on this issue?

The Good Manufacturing Practice Regulations, specifically 21 CFR 211.110(a) state that written procedures shall include in-process controls or tests on "appropriate samples" to ensure "adequacy of mixing to assure uniformity and homogeneity." Concerning "appropriate samples", there are two issues: 1.) obtaining an accurate sample and 2.) taking the sample at the appropriate time.

- 1.) **Accurate samples.** Obtaining an accurate sample is difficult because of the range of particle sizes present in the blend. If one uses a sample thief to sample from a variety of locations in a blender there is the possibility that the analytical result can be biased due to segregation occurring when the material flows into the sample device. Another factor that can cause erroneous blend test results is the tendency for some actives to acquire a static charge during blending. Statically charged particles will interact with the sampling device to bias the result. All of this is overcome when a finished tablet or capsule is tested for Content Uniformity.
- 2.) **Appropriate sample time.** The regulations [21 CFR 211.110(c)] call for the testing of in-process materials during production "at commencement or completion of significant phases [of production]." This raises another issue with the appropriateness of blend testing as an in-process test. The guidance requires BUA sampling from the blender; however, blending continues every time the material is transferred from one container to another. The process of blending is not complete until the granulation flows into the die cavity or capsule shell. As mentioned before, the Content Uniformity test also tests for blend uniformity at the end of the blending stage.

It is interesting to note that the other listed solid dosage form in-process controls and tests mentioned in 21 CFR 211.110(a) are...

1. Tablet or capsule weight variation;
2. Disintegration time; and
3. Dissolution time and rate.

All of these tests must be performed on the finished dosage form (tablet or capsule). Content Uniformity testing of the finished dosage form is the only "appropriate sample" to ensure "adequacy of mixing to assure uniformity and homogeneity."

Thank you for your time and consideration of our comments on this Guidance.



Larry Boos, Ph.D.
President & CEO

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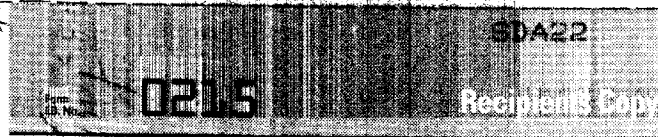
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